IN THE UNITED STATES DISTRICT COURT FOR THE MIDDLE DISTRICT OF TENNESSEE NASHVILLE DIVISION

RUTH SMITH, Individually and as Widow for the Use and Benefit of Herself and the Next of Kin of Richard Smith, Deceased, Plaintiff, v. PFIZER INC., *et al.,* Defendants.	)	Civil No. 3:05–0444 Judge Aleta A. Trauger

TRIAL TESTIMONY OF SHEILA WEISS SMITH, PHD

My name is Sheila Weiss Smith, and I am a Professor in the Departments of Pharmaceutical Health Services Research, School of Pharmacy and Epidemiology & Preventive Medicine, School of Medicine, and Director of the Center for Drug Safety at the University of Maryland Baltimore. I also hold appointments at the Veteran's Administration (Research Associate) and the Department of Epidemiology, Johns Hopkins University's Bloomberg School of Public Health (Visiting Professor). I am a fellow of the International Society of Pharmacoepidemiology. Over the past decade, I have served as a voting member on a number of advisory committees for the United States Food and Drug Administration (FDA), when epidemiologic expertise was needed. My expertise and professional accomplishments are more fully documented in my original expert report dated: December 20, 1997.

My research efforts and writings have focused on the area of pharmacoepidemiology, and I have written on the epidemiology of the risks associated with prescription medications with a special emphasis on methodology. I have considerable expertise in drug safety, including the evaluation of post-market spontaneous adverse event reports that are made to pharmaceutical companies and/or FDA. This evaluation often includes "data mining." Data mining is a term that describes how epidemiologists use of mathematical and statistical techniques to sift through large amounts of data to find associations that are not random or not as expected. I was recently Co-Principal Investigator of a one-half million dollar grant "the value of data mining", which is an extensive look at the comparative validity of data mining methods in the FDA's adverse reporting database, current industry practices in data mining, and factors that influence the results of data mining. Additionally, I have been Co-Principal Investigator of two sequential NCI contracts to look at the strength of the scientific evidence for cancer prevention and cancer promotion among commonly used medicines and nutraceuticals, and to estimate the potential public health impact. I am currently an investigator on an NCI-funded grant on drug safety. I recently finished a project for FDA on risk evaluation and mitigation strategies for pharmaceuticals.

I have published more than 30 peer-reviewed papers (with in excess of 570 citations), a number of which in high impact journals including New England Journal of Medicine, British Medical Journal, and Pharmacoepidemiology and Drug Safety (PDS). I am author or coauthor of more than 50 scientific presentations/posters and have given approximately 30 invited talks. I am an active member of the International Society of

Pharmacoepidemiology; participating in annual meetings, chairing sessions, reviewing abstracts, and serving on a number of committees. I have also held elected positions including membership on the board of directors.

Currently, I teach a course "advanced topics in pharmacoepidemiology", an advanced level doctoral course which is offered biannually. This has been taught simultaneously at the University of Maryland and at the FDA. This class involves advanced concepts in the design and interpretation of studies, including pharmacovigilance and data mining. I also co-teach a course in epidemiology to the pharmacy students and a course in Pharmacoepidemiology at Johns Hopkins University annually. I regularly lecture in pharmacoepidemiology and epidemiology courses run by other faculty at the University of Maryland and at Yale University; this year I taught the entire pharmacoepidemiology course at University of Maryland.

I have served as a special government employee for the FDA, over a span of more than a dozen years, and participated on a number of FDA advisory committees as a voting member. Most recently, in 2009, I served on the FDA's anti-infective drug advisory committee on Advanced Life Sciences Holding, Inc.'s application for the approval of their antibiotic, cethromycin.

I have reviewed grant proposals for the FDA, AHRQ, CDC, NIH, and EMEA and serve as a peer-reviewer for a large number of journals including American Journal of Epidemiology, Lancet, British Medical Journal, and PDS. I am on the editorial board

of the Journal of Research in Social and Administrative Pharmacy and a former member of the Isotretoin Scientific Advisory Board.

My experience and training are summarized in my CV, and it is marked as **EXHIBIT 7429.**

In this litigation, I understand that plaintiffs are claiming that spontaneous adverse event reports can be used as evidence of general causation as well as a signal that should have led the company to issue a warning pertaining to an increased risk of suicidal behavior in patients taking Neurontin. I was asked to review the spontaneous adverse event reports in the FDA AERS database to analyze any potential increased reporting of suicidal behaviors with Neurontin. As a result of my review and analysis in this litigation, I have been able to form opinions to a reasonable degree of scientific certainty as to the use of spontaneous adverse event reports to analyze any potential increased reporting of suicidal behaviors with Neurontin. I have prepared a slide summarizing my opinions in this matter. **[SHOW DEMONSTRATIVE: DR. WEISS' OPINIONS]**. First, Adverse event reports cannot reliably be used to establish a causal relationship between gabapentin and suicide. Second, the FDA's AERS database does not support the finding of a signal for completed suicide or suicide attempt. Third, Dr. Blume's methodology for reviewing AERS data is flawed and not generally accepted. Fourth, the information in the AERS database for gabapentin and suicide is unreliable and therefore uninterpretable.

Before going into my analysis, I want to first define what is meant by the term pharmacoepidemiology. Epidemiology is the study of the incidence, causes, and effects of diseases in populations. In short, epidemiology concerns how often diseases occur and in whom they are likely to occur. This area of study helps us to identify and hopefully prevent diseases in certain populations of people. Pharmacoepidemiology is the study of the use and effects of medical products (drugs, biologicals, and medical devices) in human populations. In other words, all medicines have side effects and potential hazards. Pharmacoepidemiology is the branch of epidemiology that looks for side effects –often rare effects associated with the use of medicines. Pharmacoepidemiology has emerged as a unique branch of epidemiology over the past several decades, distinguished from other field by the focus on medical product as the risk factors or exposures. Pharmacoepidemiology studies of adverse drug effects are used to make important regulatory and public health judgments concerning the risks and benefits of medicines. Pharmacoepidemiological investigations utilize the methods and study designs of epidemiology.

To form my opinions in this case, I performed an analysis of the FDA AERS database. AERS stands for Adverse Event Reporting System. It is a database where FDA stores adverse events that are reported for all approved medicines in the U.S. In order to monitor the safe use of pharmaceuticals, the FDA considers reports of serious adverse events by healthcare providers and their patients as well as mandatory reporting of events by manufacturers. These reports are called spontaneous reports, which are nothing more than a clinical observation that occurs in real-world use of the drug. In the United States,

the source of most reports is doctors and patients. The generation of these reports is known as "passive safety surveillance" method. Beginning in the late 1960's, FDA began to computerize adverse event reports, and in 1997 the old system known as the "Spontaneous Reporting System" was replaced with AERS, which is a computerized information database that FDA uses in its own post-market safety surveillance program for all approved medicines. The objective of the FDA post-marketing surveillance is to provide early detection of signals of serious and previously unknown safety issues with marketed drugs. **[SHOW DEMONSTRATIVE: SAMPLE MEDWATCH FORM]**. This slide shows a sample form that is used for submitting adverse event reports by physicians; pharmaceutical companies use a similar form.

Although I routinely perform analyses of the AERS data in the course of my research, it is very important to know that there are a number of biases and important limitations inherent in the information that is contained in the AERS database. When I say "biases", I use it in the statistical sense. Bias is a factor that results in two groups being treated differently. The presence of bias can, and often does, result in a flawed study that leads erroneous conclusions.

Medical products are regulated by government entities; they are approved for a specific use or indication with specific dosing and instructions for use. Exposures to medical products are made consciously, for the treatment of a known medical condition or to prevent or delay the occurrence of a disease. The deliberate nature of medication choice,

often introduces biases into observational studies, which can make comparisons of exposed with a comparison drug or no drug (unexposed) inappropriate.

The most common of these biases is called "confounding by indication." This means that the event that is reported and stored in the database is due to the underlying condition, or somehow related to that condition, rather than a direct effect of the drug. For example, one of the most common adverse events reported for Rogaine, a medicine for treatment of baldness is, in fact, loss of hair. The result of this is that there may be more reports of loss of hair for Rogaine compared to other medicines. So, the underlying condition of hair loss, which prompted the use of Rogaine in the first place, "confounds" a finding of increased reporting of hair loss with Rogaine. Another example would be increased reporting of pain for medicines used to treat patients with chronic pain. FDA recognizes the fact that these biases are inherent in the AERS database. FDA has written in one of its guidance documents that "Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different designs." I have provided some simple examples of bias. Bias, however, are inherent in adverse event reporting in far more subtle ways. That is why the analysis of adverse event reports and the use of large databases for this purpose requires clinical judgment and consideration of the context in which the reports are made.

Now, I would like to talk about the limitations of the AERS data. The major limitations of AERS reflect the fact that the data are generated in an uncontrolled and incomplete manner. The quality of adverse event reports is highly variable and critical information is often missing. The majority of adverse event reports have come from practicing physicians and pharmacists who may or may not notify the manufacturer or FDA when they observe an adverse event. It appears that physicians generally do not report adverse events. Historically, the proportion of events that is actually reported to FDA have been estimated at 1 – 10%, although there are concerns of the validity of these estimates and the actual reporting rates are unknown. It is generally agreed that factors such as the type and nature of the event, the drug or combination of drugs being used, the length of time the drug has been on the market, and publicity in the lay or professional press about the drug, the class of drugs, or a particular outcome all influence whether or not something is reported. Because of these biases, the number of the reports in AERS is not representative of the number of events or the rate at which adverse events occur. As I will explain later, publicity, including plaintiffs' counsels' advertising for clients to sue Pfizer over Neurontin and other litigation activities likely played a major role in the reporting of suicidal behavior events for Neurontin. Because of these limitations, adverse event reports are primarily useful for generating questions called hypothesis generating, rather than answering questions about drug safety using the more rigorous hypothesis testing, which is used in scientific studies and experiments.

Why then did I perform an analysis of the FDA AERS database in this case? Plaintiffs' expert, Dr. Cheryl Blume, performed what she called "data mining" of the AERS

database. I am of the opinion that she did not perform her analysis correctly and she did not perform a complete analysis. I wanted to see what a proper analysis of this database would show. My goal for this analysis was that I simply wanted to evaluate whether the AERS data would show increased reporting for Neurontin for completed suicide or suicide attempt. That is where my analysis was to stop – I did not conduct any clinical evaluation of the AERS data for a potential signal, as that takes clinical training and expertise that neither I nor Dr. Blume possess.

Although I was asked by counsel for Pfizer to conduct an evaluation of the analyses performed by Dr. Blume, I performed this analysis without any input from counsel, or from anyone else for that matter.

As I mentioned earlier, data mining is the use of statistical methods to quickly process large databases of adverse events and identify otherwise unexpected relationships between a drug and an adverse event (drug-event pairs) or a drug-drug interactions (drug-drug-event). Data mining differs from a scientific study, in that data mining is purely exploratory, while scientific studies are designed to test one or more predefined hypotheses. Drug-event pairs are identified by data mining as being statistically linked, such that they are more commonly found together in the database then would be expected compared to a specified background rate. **[SHOW DEMONSTRATIVE: DATA MINING CANNOT ESTABLISH CAUSATION]**. In a case series, a clinical specialist evaluates a group similar of adverse event reports and uses their clinical judgment to consider the possibility that a drug may have caused the event being

reported. This clinical judgment leads to a hypothesis, which is called a "signal." In data mining, the terms "alerts" or "signals of disproportional reporting" (SDR) are often used to distinguish it from a clinical "signal." **[SHOW DEMONSTRATIVE: CLINCAL JUDGMENT NECESSARY FOR REVIEW OF DATA MINING]**. This slide shows a quote from a letter published in JAMA by Dr. Brian Strom, a well-known expert in the area of pharmacovigilance. He wrote: "Proper interpretation also requires clinical judgment before one even considers there to be a signal." An alert or SDRs is purely a statistical association. It may or may not be clinically meaningful.

It is important to point out that Dr. Blume did not perform either a statistical or a clinical evaluation of the adverse event data she summarized. So, it is my opinion that what she claims to have found from the AERS database is not a "signal." This is because she did not perform the data mining analysis correctly. But, even if you assume that the analysis was performed correctly, she cannot say there is a signal because she was not able to clinically review the data. She only shows the proportion of reports that included those events that she chose to look at for a variety of drugs. Such data, in and of themselves, are not meaningful, because reporting can vary for any number of reasons that are unrelated to the safety of the drug.

I would now like to discuss my analyses, which were prepared in 2007 and 2008. In the AERS database there were 30,528 adverse event cases where the drug gabapentin or Neurontin was mentioned by the reporter as the suspect drug or another drug being taken at the same time. It is important to remember that there are two meanings to the term

"suspect." The reporter suspected the medicine as being related to the outcome. A manufacturer reporting an event for a patient taking one or more of its medicines must list all of its medicines as suspect. **[SHOW DEMONSTRATIVE: GABAPENTIN SPONTANEOUS REPORTS OVER TIME]**. In AERS, more than 50% of cases were reported after 2003, 10 years after Neurontin was approved. The number of spontaneous reports for Neurontin appears to have peaked in 2005, which is well after the time of introduction of publicity bias as a result of litigation. At this point in the analysis, these data do not mean much. These numbers need to be put into perspective, and that is done using data on the number of patients exposed to gabapentin.

In order to estimate exposure, FDA routinely uses prescription data. Prescription sales data are necessary to put the adverse event reporting trend into perspective in that it provides an estimate of patient exposure and how it changes over time. **[SHOW DEMONSTRATIVE: NEURONTIN/GABAPENTIN PRECRIPTIONS OVER TIME]**. As this slide shows, Neurontin was widely marketed and used in more than 12 million patients by 2005. Prescriptions for the gabapentin (brand and generic) have increased over time from 243,528 prescriptions in 1993 to an estimated 16.7 million in 2006. When I couple these data with the gabapentin spontaneous reports I showed you in the previous slide, here is what I see. **[SHOW DEMONSTRATIVE: GABAPENTIN REPORTS AS A PERCENTAGE OF TOAL PRESCRIPTIONS]**. This slide shows that as the total prescriptions increased to over 16 million per year from 2003 onward, the proportion of adverse events in relation to sales dropped to 0.018% in 2003. **[SHOW DEMONSTRATIVE: GABAPENTIN REPORTS DECREASE AS**

PRECRIPTIONS INCREASE]. Thus, as patient exposure to Neurontin increased over time, the proportion of adverse events relative to this exposure declined.

I then repeated the search of the FDA AERS database to cases in which gabapentin was noted by the reporter as the "suspect" drug, regardless of whether there other medications listed. When you have a medicine that is widely used, you tend to get a lot of adverse events reports. I used suspect here to try to refine my analysis to events where the reporter felt the event was related to the medicine. I should point out here that a label of "suspect" does not mean that there has been a conclusion that the medicines caused any or all of the reported events. **[SHOW DEMONSTRATIVE: PROPORTION OF REPORTS IN WHICH GABAPENTIN WAS 'SUSPECT'].** This slide shows that the proportion of total cases in which gabapentin was selected as the suspect drug was highest in the first three years of marketing and then tapered off rapidly. It stayed at less than 50% since 2001

I then analyzed adverse events based on how the events were reported to FDA. Reports are characterized into three types by the how they are received and the speed of reporting: direct, expedited and periodic. Direct reports are those which are sent directly to the FDA by the reporter, such as consumers, physicians, and lawyers, through the MedWatch Program. Expedited and periodic reports are sent to the FDA through the manufacturer, with expedited (or 15-day reports) being serious and unexpected events which must be reported within 15-days of the manufacturer becoming aware of the event. **[SHOW DEMONSTRATIVE: GABAPENTIN REPORTS BY REPORT TYPE – BY**

YEAR]. This slide shows that in each year from 1999 through 2006, the total number of gabapentin reports increased, with a peak in 2005. You will note that after mid-2003 the graph is shaded to show when the adverse event data base was corrupted by attorney advertising and publicity surrounding the litigation.

The results shown here are also consistent with the increased use of gabapentin, as well as an overall increase in adverse event reporting to FDA for all drugs. What is remarkable is a dramatic jump in the number of direct reports in the year 2005. From 1994 – 2004, the number of direct reports increased from 28 to 130. From 2004 – 2005, the number of direct reports jumped to 595 reports. Thus, in just one year, the number of direct reports increased as much as it had over the previous 10 years. In the AERS database, direct reports typically account for just 10% of all reports.

To explore further and understand why there was a sudden and dramatic increase in direct reports in 2005 with gabapentin as the suspect agent I looked at the distribution of reports each quarter (based on report date) by the patient outcome. **[SHOW DEMONSTRATIVE: GABAPENTIN REPORTS BY REPORT TYPE – BY QUARTER]**. This slide shows that there was a very large number of deaths reported (n=315) in the first quarter of 2005. Over the entire time of marketing, the overall proportion of deaths was less than five percent, but in the first quarter of 2005 it was 20%. This plot does not mean that all of these people died in the first quarter of 2005; this only shows report date, not event date.

In an attempt to try to explain these findings, I examined individual events by report date. I found it unique and suspicious that a large number of reports were all entered into AERS within a 4 day period in 2005. Also, the reports were unusually "clean" with 1 or 2 reaction terms listed, when an infinite number are allowed by FDA; the average is 4 per report. Most, if not all, listed as "Neurontin" where reports from other time periods have both Neurontin and gabapentin. Most had only Neurontin listed – without listing any other medications - which is unusual for Neurontin users. These reports are highly suspicious and very unreliable for analysis purposes. This demonstrates that these peaks after the introduction of litigation and associated publicity were stimulated and therefore not valid for any analytical purpose. Dr. Blume has conceded that after 2003 these reports are impacted by publicity.

As part of my analyses, I calculated the Proportional Reporting Rate or PRR for completed suicides and suicide attempts reported for Neurontin and/or gabapentin. A PRR is a calculation of whether a particular drug-event combination is reported more often together than expected. It does this by "generating a score by comparing the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the "observed reporting fraction") with the fraction of reports for the same particular event for all drugs ("the expected reporting fraction"). This is not the same analysis that Dr. Blume performed. What she presented was merely the percentage of reports for Neurontin and other drugs, but this is not a PRR.

Although Dr. Blume looked at many events in addition to completed suicides and suicide attempts, I chose to look at only completed suicides and suicide attempts. These terms are less ambiguous than the additional terms that Dr. Blume used in her analysis. Completed suicide and suicide attempt are clearly serious under the regulatory definition, where serious is based on patient outcome and not the reaction terms coded. Under the FDA regulations, "serious" is defined as events that lead to death, hospitalization (initial or prolonged), life threatening, persistent or significant disability, birth defect, or an important medical event that would have resulted in any of these outcomes if not for medical or surgical intervention. Terms like suicidal ideation or suicidal thoughts may not always meet this criterion. This approach is consistent with the methods that I use in my professional practice.

In the field of pharmacoepidemiology, a PRR greater than 2, along with several other statistical criteria, is a commonly used statistical threshold to define an alert. **[SHOW DEMONSTRATIVE: PRR FOR GABAPENTIN: COMPLETED SUICIDE AND SUICIDE ATTEMPT]**. This slide shows the results of an analysis comparing completed suicide or suicide attempt for gabapentin to those events reported for all other drugs. As shown in this slide, completed suicide and suicide attempt did not reach the threshold of 2.0 until after 2005. As shown by the shading, this occurs after the publicity bias generated by litigation activities. This means that there is no data mining alert for suicide with Neurontin using the AERS data until that time.

You can see from this plot that the PRR does eventually rise above 2. It is almost certain that the PPR increased, in part, as a result of the 258 direct reports submitted in first Quarter 2005 by attorneys, as confirmed in a letter from Mr. Finkelstein (plaintiffs' attorney) to Dr. Katz of FDA that he submitted these 258 reports. **[SHOW DEMONSTRATIVE: 4/12/2005 LETTER FROM KATZ TO FINKELSTEIN].** This is a good example of how bias, here created by plaintiffs' attorneys who submitted a large number of stimulated reports, can decrease the usefulness of the data in the AERS database to identify signals. There is evidence of significant bias in the reporting of suicides to the FDA's adverse event database, which can be attributed to the plaintiffs' attorneys. So, basically, plaintiffs' attorneys have created this very "signal" in the AERS database. As highlighted in this letter from FDA to plaintiffs' counsel, FDA recognized the flaws in the FDA AERS database and the uninterpretable nature of spontaneously reported suicide events. I agree with FDA's conclusion as to the problems with the use of adverse event reports for this purpose.

I then performed a PRR calculation where I compared reports of completed suicide for gabapentin to the same event reported for the other 10 AEDs analyzed by FDA in its 2008 meta-analysis. **[SHOW DEMONSTRATIVE: GABAPENTIN VERSUS FDA AEDS]**. This slide shows the PRR values, by year. As you can see, the PRR was less than 1.0 until 2006, which means that the reporting of completed suicide for Neurontin was less than the reporting of completed suicide for the other 10 AEDs analyzed by FDA. This provides additional evidence that there was no signal of increased reporting of suicide for gabapentin. Analysis of suicide attempts yields a similar result.

Plaintiffs have suggested that there was no notoriety bias in reporting of suicides based solely on the timing of plaintiffs' counsel's reporting of suicide events to FDA. However, this ignores the fact that there are many other people and entities reporting events to the FDA. Indeed, the evidence suggests that there was significant "notoriety bias" surrounding the reporting of suicide-related adverse events during the period in question. **[SHOW DEMONSTRATIVE: COMPLETED SUICIDE REPORTS NEURONTIN VERSUS ALL DRUGS]**. This slide shows the number of completed suicides in the FDA AERS database for all drugs (red line) and for gabapentin only (blue line). This shows that the number of suicides (completed suicides) reported to the FDA regardless of drug more than doubled from 1027 in 2002 to 2119 reports in 2003, while suicide reports mentioning gabapentin increased 2.3-fold from 40 in 2002 to 92 in 2003. The reporting of completed suicides (all drugs) appears to have peaked in 2005 at 2899 reports. Also during this same time period both the FDA and European regulators issued warnings about a possible link between SSRI antidepressants and suicidal behaviors in children and adolescents in 2003 and FDA held an advisory committee meeting on this subject in early (February 3rd) 2004. Such events are known to stimulate reporting. This is an important example as to why an epidemiologist needs to consider much more than simply raw counts of adverse events for a single drug that gives the appearance of a peak or spike on a graph. While visually interesting, such peaks and spikes of adverse event reports need to be considered carefully and in the appropriate context. As this graph shows, Neurontin is no different than what is being reflected in the entire AERS database with regards to reports of suicide.

In conclusion, it is my opinion, to a reasonable degree of scientific certainty that adverse event reports cannot reliably be used to establish a causal relationship between gabapentin and suicide, and the information in the AERS database for gabapentin and suicide is unreliable and uninterpretable. It is also my opinion, to a reasonable degree of scientific certainty, that the FDA's AERS database does not support the finding of a signal for completed suicide or suicide attempt with Neurontin. Although plaintiffs' experts have claims to have found a signal, their methodology for reviewing AERS data is flawed and not generally accepted.